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(54) Title: PHARMACEUTICAL COMPOSITION CONTAINING ITRACONAZOLE WITH GASTRIC pH-INDEPENDENTLY IMPROVED SOLUBILITY AND PREPARATION METHOD THEREOF

(57) Abstract: The present invention relates to a pharmaceutical composition containing itraconazole and its preparation, more particularly, to a pharmaceutical composition containing itraconazole obtained by dissolving, followed by spray-drying, and its preparation. The pharmaceutical composition containing itraconazole according to the present invention can increase the solubility of itraconazole and prevent the reduction of solubility of itraconazole caused as pH increases. As a result, the pharmaceutical composition of the present invention can improve the bioability of itraconazole and minimize absorption variance dependent on pH of the individual's stomach. Also, the pharmaceutical composition can be prepared by a single-process, i.e., a spray-spraying, such that it can be prepared in a economic manner.

**PHARMACEUTICAL COMPOSITION CONTAINING ITRACONAZOLE WITH
GASTRIC pH-INDEPENDENTLY IMPROVED SOLUBILITY AND PREPARATION
METHOD THEREOF**

5 FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition containing itraconazole and a method for preparing the same. More particularly, the present invention relates to an itraconazole-containing
10 pharmaceutical composition and to a preparation method, which comprises the steps of:

- 1) dissolving into a solvent itraconazole, a pH-independent water-soluble polymer and, optionally, a pharmaceutically acceptable additive; and
15 2) spray-drying the obtained solution.

BACKGROUND OF THE INVENTION

Itraconazole is a compound known as an antifungal agent. Despite its powerful medicinal effect, it has very low
20 solubility in water such that very scrupulous techniques are required to prepare a dosage form. It was observed that lower pH increased the solubility of itraconazole into water. But, the observed solubility of itraconazole into water was only 1 µg/ml or less even in a strong acidic condition (e.g.,
25 pH 1.2).

For drugs that have a very low solubility into water, such as itraconazole, it was also known that rate-determining step in absorption are largely affected by their solubility rather than by other factors such as drug

dissolution, disintegration, and the like. That is, such a drug, although being perfectly eluted or disintegrated, is barely dissolved into body fluid due to its low solubility and thus, its absorption efficiency is utterly poor.

5 It was reported that the solubility of commercially available formulations containing itraconazole into body fluid is drastically reduced by even a small increase of pH. For example, PCT/KR99/00854 disclosed that the solubility of conventional itraconazole formulations having pH 2.4 is as
10 much as 5.3 fold lower than that of pH 1.6. Based on this founding, it is suggested that the pH-dependent solubility of itraconazole results in the variations in absorption between individuals. The founding that an individual who does not secrete sufficient amounts of gastric acid has a
15 difficulty in absorbing itraconazole supported this suggestion. As for AIDS patients, for example, even when their gastric pH values are elevated owing to their insufficient secretion of gastric acid, their absorption of itraconazole is reported to be no more than 50 % of that of
20 normal person (Smith D, Van De Velde V, Woesienborghs R, Gazzard BG, The pharmacokinetics of oral itraconazole in AIDS patients, *J. Pharm., Pharmacol.*, 44, 1992, p618-619). In practice, for such patients, an itraconazole-containing formulation should be orally administered together with a
25 beverage that can reduce the gastric pH, such as cola. Or, it is recommended that a commercially available itraconazole-containing formulation be administered after meals because increase of the gastric pH can significantly reduce the absorption of itraconazole.

Considering the above report together with the research results in which normal adults have a pH of about 1 to 3.5 in the stomach and 16 % of adults are revealed to have gastric pH of over 3.0, pharmaceutical compositions comprising itraconazole must be designed such that itraconazole solubility is not greatly changed with gastric pH fluctuation, thereby maximizing drug absorption with concurrent minimization of intra- and inter-individual absorption variation of itraconazole (The design and evaluation of controlled release systems for the gastrointestinal tract In: Advances in drug delivery systems, J. M. Anderson and S. W. Kim eds., Elsevier, Amsterdam, 1986, 27-38; Comportment pharmacocinetique des spheroides: apport et interet en clinique-Proceed. Symp. Capsugel, Paris, 1987, 73-81). In consequence, in order to improve the *in vivo* absorption of itraconazole, it is required for the itraconazole-containing formulation to have high solubility into human body and to have an independency in pH fluctuation.

20

Up to now, there have been many attempts and studies for improving the solubility of itraconazole into water to increase its *in vivo* absorption and availability. For example, WO 85/02767, US 4,764,604 and WO 95/08993 disclosed that the water solubility and bioavailability of itraconazole could be increased by the inclusion of itraconazole into cyclodextrin.

WO 94/05263 and KR 95-702826 disclosed a bead dosage form of itraconazole formed of water-soluble polymer, and WO

93/15719 reported an itraconazole-containing formulation for topical administration using liposomes.

In the last few years, a method for increasing the solubility of itraconazole by spray-drying (WO 98/57967, KR 5 99-1564) and a method for increasing the bioavailability of itraconazole by obtaining its molten form (extrudate) in combination with water-soluble polymer (WO 97/44014) have been developed.

In the melt (extrusion) method described in WO 97/44014, 10 which is one of the formulating techniques of itraconazole in use, the drug and a polymer are melted simultaneously, and then mixed. However, scrupulous care must be taken to control temperature, because the difference between the melting temperature of the polymer and the decomposition 15 temperature of the drug or the polymer is very small. In addition, because the temperature at which polymer begins to melt should be lower than the drug or polymer decomposes, the polymer can be used in the method is significantly narrowed, that is, the polymer with higher average molecular 20 weight can not be used. Further, the heat generated during the pulverization of the molten product to final fine particles may cause recrystallization of the drug, which considerably increases the size up to 600 μm with a wide particle size distribution and does not afford particles 25 having uniform size. The dissolution of drugs is, generally, proportional to the specific area of particles, and thus, this may be problematic.

Irrespective of their sizes, the particles, which undergo pulverization in the melt (extrusion) method are

aggregated and resulted in the reduction of wet ability and thus, needed vexatious process further in the method.

Most of the methods developed so far, to improve the bioavailability of itraconazole, are aimed at increasing the solubility of itraconazole itself, but do not address the problem of the solubility drop attributed to pH increase. Therefore, there remains a need for dosage forms that can surmount the absorption difference of itraconazole resulting from the intra- or inter-individual variations of gastrointestinal physiology.

SUMMARY OF THE INVENTION

Leading to the present invention, the intensive and thorough research of the present inventors, which has been conducted to develop itraconazole dosage forms that are improved in the water solubility of itraconazole and in the solubility difference based on pH change, resulted in the finding that spray-drying the itraconazole in combination with pH-independent water-soluble polymer can produce fine particles with improved the water solubility and a significantly reduced pH dependency.

Therefore, it is an object of the present invention to provide an itraconazole-containing pharmaceutical composition, whose water solubility is improved and pH-independent.

It is another object of the present invention to provide a method for preparing such an itraconazole-containing pharmaceutical composition.

It is still another object of the present invention to provide a dosage form prepared from the itraconazole-containing pharmaceutical composition by an ordinary pharmaceutical method.

5 In order to achieve these and other objects described in the detailed description, there are provided an itraconazole-containing pharmaceutical composition and a method for preparing the same, which comprises the steps of:

- 1) dissolving into a solvent itraconazol and, a pH-
10 independent water-soluble polymer; and
- 2) spray-drying the obtained solution.

In addition, the present invention provides a dosage form formulated from the itraconazole-containing
15 pharmaceutical composition by an ordinary pharmaceutical process.

The present invention pertains to a dosage form of itraconazole, in which itraconazole shows more improved bioavailability and *in vivo* absorption with retaining its
20 therapeutic effect over the wide gastric pH range.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, itraconazole, which is poor in gastrointestinal absorption due to its low
25 water solubility, is spray-dried, together with at least one water-soluble polymer, to improve the solubility of itraconazole into water and has a superior pharmaceutical efficacy even on the condition of increased pH within the stomach.

The polymer used in the present invention can be selected such that it can be applied to the spray-drying. The conditions considered in the choice of the polymer used in the present invention are as follows: the viscosity of the spray dried solution, the content of the solid in the spray dried solution, the shape and flowability of the spray-dried product, and the particle size and particle size distribution of the spray-dried product. Additionally, when the final spray-dried product is formulated into tablets or capsules, it is important for the dosage forms to have the physical properties satisfying the pharmaceutical requirements, such as disintegration and dissolution, as well as not to lose such pharmaceutical features during the formulation. The reason is that the spray-dried product, even if showing high solubility, is very difficult to commercialize if it possesses pharmaceutical property that inhibits the absorption of itraconazole into the body.

According to the present invention, therefore, there are provided a novel pharmaceutical formulation and the method for the same wherein the spray drying condition and other conditions optimized for improving both the solubility of itraconazole and pharmaceutically administrable properties for itraconazole are specified.

Suitable polymer used in the present invention is hydrophilic polymer. When being subjected to spray drying, along with itraconazole, the polymer functions to make the itraconazole disordered in crystalline structure, thereby minimizing the activation energy necessary for the dissolution of the drug, as well as establishing hydrophilic

conditions around the drug molecules, thereby improving the solubility of the drug itself.

Particularly preferable polymer is a pH-independent polymer which having relatively constant solubility
5 irrespective of pH change. In light of the tendency of itraconazole to have higher solubility in more acidic conditions, polymers that can be dissolved in alkaline conditions, such as methacrylates (e.g., Eudragit LTM) and hydroxypropylmethyl cellulose phthalate (HPMCP), are not
10 appropriate in the present invention because they inhibit acidic solvents from reaching the itraconazole surrounded, thereby resulting in a decrease in the solubility of the itraconazole. Polymers that can be dissolved in acidic conditions, such as aminoalkyl methacrylates (e.g., Eudragit
15 ETM) and polyvinylacetal diethyl aminoacetate (e.g., AEA), contrary to expectation, are also unsuitable for use in the present invention because their solubility is reduced by even a small increase of pH even though the overall pH condition still remains acidic. Hence, pH-dependent
20 polymers are undesirably dissolved at different rates over the gastric pH range. In contrast, the pH-independent polymer is drastically decreased in viscosity as pH moves toward extreme acidic regions, so that the structure of the itraconazole-containing particles becomes flexible enough to
25 allow water to penetrate therein.

Examples of preferable pH-independent polymer include cellulose derivatives, such as methyl cellulose, ethyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropylmethyl cellulose,

carboxymethyl cellulose, sodium carboxymethyl cellulose, and
carboxymethylethyl cellulose; polyvinyl alcohols;
polyvinylpyrrolidone or copolymers thereof;
polyvinylacetate; polyalkeneoxide or polyalkeneglycol;
5 polyethylene-polypropylene copolymers; and polyoxyethylene-
co-polyoxypropylene copolymer (Poloxamer); and combinations
thereof.

Preferably, the pH-independent water-soluble polymers
can be used in the amount of 10 to 1,000 part by weight
10 based on itraconazole.

Compared to itraconazole alone, a combination of
itraconazole and the polymer, prepared by the spray-drying
method, has an increased solubility into water. In view of
solubility, the cellulose derivatives and poloxamer are more
15 preferable. Among the cellulose derivatives, methyl
cellulose, hydroxypropylmethyl cellulose and hydroxypropyl
cellulose are the most preferable, since they remarkably
increase the water solubility of itraconazole, particularly
at around pH 2.4.

20 The above polymers are generally commercialized in
various grades based on average viscosity or molecular
weight. In the case of hydroxylpropylmethyl cellulose, for
example, 2 % aqueous solutions ranging in average viscosity
from 3 to 100,000 cps are commercially available.
25 Commercially available polyethyleneoxide, one of
polyalkeneoxides, can range in average molecular weight from
100,000 to 7,000,000.

On the whole, the average viscosity of the polymer,
dependent on its average molecular weight and molecular

weight distribution, determines the physical properties of the final products prepared therefrom. For instance, when it is designed a prolonged release type formulation with hydroxypropylmethyl cellulose, the release rate is slower as
5 higher viscosity of polymers is used. When being used as a binder, the higher viscosity of polymers shows the stronger binding forces.

Generally, differences in the average viscosity of the polymers used affect the physical properties of the final
10 products prepared by dry-spraying itraconazole, as an insoluble drug, in combination with the polymer. In detail, polymer with higher average viscosity, in spite of same one, confers higher solubility or greater dissolution of the drug. For instance, at pH 1.6, itraconazole is increased in water
15 solubility by factors of 1.3 times and 1.5 times when being spray-dried in combination with hydroxypropylmethyl cellulose with average viscosity of 6 and 15 cps, respectively, compared to when being spray-dried in combination with hydroxypropylmethyl cellulose with an average viscosity of 3
20 cps. The solubility difference according to the viscosity of the polymer is greatly increased at pH 2.4. For example, when hydroxypropylmethyl cellulose with average viscosity of 6 and 15 cps is used, itraconazole solubility is 1.3 times and 14.7 times higher, respectively, than when
25 hydroxypropylmethyl cellulose with an average viscosity of 3 cps is used.

However, there is a cutoff point from which the solubility of itraconazole decreases with increasing of average viscosity, rather than increases. For example,

where the hydroxypropylmethyl cellulose with an average viscosity of 50 cps or higher is used, the water solubility of itraconazole is gradually decreased. The reason why the water solubility of itraconazole is decreased at high viscosities is that, because the drug cannot readily get out of highly viscous surroundings of the polymers, it requires too much time for the drug to be completely dissolved. Additionally, polymers of excessively high average viscosity restrain the drug from eluting out to entail excessive release persistency, resulting in deteriorating the absorption of the drug by the body.

In consideration of the above-mentioned factors, pH-independent water-soluble polymers that exhibit an apparent average viscosity of 1 to 1,000 cps in a 2 % aqueous solution at 20 °C are preferable in the present invention. In cases of polymers such as hydroxypropylmethyl cellulose, hydroxypropyl cellulose and methyl cellulose, their 2 % aqueous solutions preferably have an apparent average viscosity ranging from 1 to 100 cps at 20 °C and more preferably from 10 to 60 cps.

The particle size of the itraconazole-containing pharmaceutical composition is 10 nm to 1,000 μm , which is changeable to be between 1 to 10 μm of a particle size distribution by spray drying condition as follow.

In addition to the aforementioned ingredients, the itraconazole-containing pharmaceutical composition of the present invention may comprise pharmaceutically acceptable additives. For instance, salts such as sodium chloride; saccharides such as white sugar and lactose; excipients such

as finely crystallized cellulose, calcium hydrogen phosphate, starch and mannitol; and/or lubricants such as magnesium stearate, talc, glyceryl behenate and colloidal silica may be preferably used in an amount of 50 part by weight or less
5 of the itraconazole.

Also, the present invention pertains to a method for preparing an itraconazole-containing pharmaceutical composition as a pharmaceutically active ingredient, which comprises steps of:

10 1) dissolving into a solvent itraconazole, a pH-independent water-soluble polymer and optionally, a pharmaceutically acceptable additive; and

2) spray-drying the obtained solution.

According to one aspect of the present invention,
15 appropriate excipients may be added with the aim of improving the flowability of the spray-dried products. In the present invention, a single spray-drying process is adopted thereby to bring about an improvement in aspects of economics and productivity for itraconazole-containing
20 pharmaceutical compositions.

Upon spray-drying, it must be taken of the viscosity and solid content of the spray drying solution, the shape and flowability of the spray-dried product, and the particle size and particle size distribution of the spray-dried
25 product. Additionally, when the final spray-dried product is formulated into tablets or capsules, it is important for the dosage forms to have the physical properties satisfying the pharmaceutical requirements, such as disintegration and dissolution, as well as not to lose such pharmaceutical

features during the formulation. The reason is that the spray-dried product, even if showing high solubility, is very difficult to commercialize if it possesses pharmaceutical properties that inhibit its absorption into
5 the body.

According to the present invention, therefore, there are provided the spray-drying condition and other conditions which are optimal to improve the solubility of itraconazole and to provide pharmaceutically administrable properties for
10 itraconazole.

Upon spray-drying, the properties of the final spray-dried product are greatly dependent on inlet air temperature, outlet temperature, the injection rate and spraying pressure of the spraying solution. The inlet air temperature should
15 be determined in such a range that itraconazole and the polymers are not physically and chemically changed at all. The injection rate and spraying pressure of the spray drying solution should be sufficiently considered the drying capacity of the spray-drier used. In particular, since the
20 outlet temperature is most closely related to the optimization of the total process, care must be taken of its control. The higher the spraying pressure is and the lower the solid content of the spray-drying solution is, the smaller the particle size of the spray-dried product is.
25 Higher inlet and outlet temperatures improved the flowability of the particles, but resulted in increasing the bulk density of the particles. In general, as particle size becomes smaller, it has a larger specific area, showing a higher dissolution rate or solubility. In the present

invention, however, spray-dried products containing a large quantity of fine particles of several nm are rather decreased in solubility owing to inter-particulate agglomeration or aggregation.

5 By precisely optimizing the spray-drying conditions, particle size of the spray-dried products can be controlled. In particular, the method for preparing a itraconazole-containing pharmaceutical composition as a pharmaceutically active ingredient, comprises the steps of:

10 1) dissolving into a solvent itraconazole, a pH-independent water-soluble polymer, and optionally a pharmaceutically acceptable additive; and

2) spray-drying the solution under the conditions including

15 a spray-drying injection rate of 40 ~ 700 ml/min,
a spray-drying pressure of 0.5 ~ 7 kg/cm²,
a spray-drying inlet air temperature of 90 ~ 250 °C,
a spray-drying outlet temperature of 40 ~ 150 °C, and
a solid content of the spray-drying solution of 0.5 ~
20 20.0 %.

Suitable for use in the spray drying is a single or mixed solvent system composed of dichloromethane, chloroform, ethanol and/or methanol.

Further, the present invention pertains to a dosage
25 form of the itraconazole-containing pharmaceutical composition. In this regard, the composition may be formulated into a tablet, a coated tablet, a hard capsule, a soft capsule, suspension, suspended syrup, dry syrup, a paste, an solution or a spray.

A better understanding of the present invention may be obtained in the light of the following examples which are set forth to illustrate, but are not to be construed to limit the present invention. It should be noted that
5 various modifications could be made within the spirit and scope of the present invention.

EXAMPLE 1: Preparation of Itraconazole-Containing
Pharmaceutical Composition 1

10

Along with 100 g of methyl cellulose and 100 g of itraconazole was dissolved in 1,750 g of a solvent mixture of ethanol and dichloromethane in volume proportions of 1:1. 1 g of talc was well dispersed in the solution to give a
15 spray drying solution. With the aid of a spray-drier (Mobile MinorTM), the spray-drying solution was spray-dried under the following conditions to prepare an itraconazole-containing pharmaceutical composition.

a spray-drying injection rate of 50 ~ 60 ml/min,
20 a spray-drying pressure of 3 kg/cm²,
a spray-drying inlet air temperature of 105 ~ 115 °C,
a spray-drying outlet temperature of 55 ~ 65 °C, and
a solid content of the spray-drying solution of 5.2 %.

25 EXAMPLE 2: Preparation of Itraconazole-Containing
Pharmaceutical Composition 2

An itraconazole-containing pharmaceutical composition was prepared in the same manner and under the same conditions as in Example 1, except that 100 g of

hydroxypropylmethyl cellulose was used instead of methylcellulose.

EXAMPLE 3: Preparation of Itraconazole-Containing
5 Pharmaceutical Composition 3

An itraconazole-containing pharmaceutical composition was prepared in the same manner and under the same conditions as in Example 1, except that 100 g of polyvinylpyrrolidone was used instead of methylcellulose.

10

EXAMPLE 4: Preparation of Itraconazole-Containing
Pharmaceutical Composition 4

An itraconazole-containing pharmaceutical composition was prepared in the same manner and under the same
15 conditions as in Example 1, except that 100 g of polyvinyl alcohol was used instead of methylcellulose.

EXAMPLE 5: Preparation of Itraconazole-Containing
Pharmaceutical Composition 5

20 An itraconazole-containing pharmaceutical composition was prepared in the same manner and under the same conditions as in Example 1, except that 100 g of polyvinylacetate was used instead of methylcellulose.

25 EXAMPLE 6: Preparation of Itraconazole-Containing
Pharmaceutical Composition 6

An itraconazole-containing pharmaceutical composition was prepared in the same manner and under the same conditions as in Example 1, except that 100 g of

polyethyleneoxide was used instead of methylcellulose.

EXAMPLE 7: Preparation of Itraconazole-Containing Pharmaceutical Composition 7

5 An itraconazole-containing pharmaceutical composition was prepared in the same manner and under the same conditions as in Example 1, except that 100 g of hydroxypropyl cellulose was used instead of methylcellulose.

10 EXAMPLE 8: Preparation of Itraconazole-Containing Pharmaceutical Composition 8

An itraconazole-containing pharmaceutical composition was prepared in the same manner and under the same conditions as in Example 1, except that 100 g of
15 polyoxyethylene-polyoxypropylene copolymer (Poloxamer) was used instead of methylcellulose.

Details of the itraconazole-containing pharmaceutical compositions prepared in Examples 1 to 8 are summarized in
20 Table 1, below.

TABLE 1

Pharmaceutical Compositions with Itraconazole as
Pharmaceutically Active Ingredient

25

Composition		Content							
		(% w/w/ of itraconazole 100)							
	Example	1	2	3	4	5	6	7	8
Drug	Itraconazole	100	100	100	100	100	100	100	100

Polymer	Methylcellulose	100	-	-	-	-	-	-	-
	Hydroxypropylmethyl cellulose	-	100	-	-	-	-	-	-
	Polyvinyl pyrrolidone	-	-	100	-	-	-	-	-
	Polyvinyl alcohol	-	-	-	100	-	-	-	-
	Polyvinyl acetate	-	-	-	-	100	-	-	-
	Polyethylene oxide	-	-	-	-	-	100	-	-
	Hydroxypropyl cellulose	-	-	-	-	-	-	100	-
	Poloxamer	-	-	-	-	-	-	-	100

EXAMPLE 9: Preparation of Itraconazole-Containing Pharmaceutical Composition 9

An itraconazole-containing pharmaceutical composition
 5 was prepared in the same manner and under the same
 conditions as in Example 1, except that 100 g of
 hydroxypropylmethyl cellulose whose 2 % aqueous solution has
 an average viscosity of 3 cps at 20 °C, was used instead of
 100 g of methylcellulose.

10

EXAMPLE 10: Preparation of Itraconazole-Containing Pharmaceutical Composition 10

An itraconazole-containing pharmaceutical composition
 was prepared in the same manner and under the same
 15 conditions as in Example 1, except that 100 g of
 hydroxypropylmethyl cellulose whose 2 % aqueous solution has
 an average viscosity of 6 cps at 20 °C, was used instead of
 100 g of methylcellulose.

EXAMPLE 11: Preparation of Itraconazole-Containing
Pharmaceutical Composition 11

An itraconazole-containing pharmaceutical composition was prepared in the same manner and under the same
5 conditions as in Example 1, except that 100 g of hydroxypropylmethyl cellulose whose 2 % aqueous solution has an average viscosity of 15 cps at 20 °C, was used instead of 100 g of methylcellulose.

10 EXAMPLE 12: Preparation of Itraconazole-Containing
Pharmaceutical Composition 12

An itraconazole-containing pharmaceutical composition was prepared in the same manner and under the same
conditions as in Example 1, except that 100 g of
15 hydroxypropylmethyl cellulose whose 2 % aqueous solution has an average viscosity of 50 cps at 20 °C, was used instead of 100 g of methylcellulose.

EXAMPLE 13: Preparation of Itraconazole-Containing
20 Pharmaceutical Composition 13

An itraconazole-containing pharmaceutical composition was prepared in the same manner and under the same
conditions as in Example 1, except that 100 g of
hydroxypropylmethyl cellulose whose 2 % aqueous solution has
25 an average viscosity of 4000 cps at 20 °C, was used instead of 100 g of methylcellulose.

Average viscosities of the hydroxypropylmethyl cellulose used in the itraconazole-containing pharmaceutical

compositions of Examples 9 to 13 are given in Table 2, below.

TABLE 2

Average Viscosity of Hydroxypropylmethyl Cellulose

5

Composition	Hydroxypropylmethyl cellulose				
Example	9	10	11	12	13
Average viscosity (cps)*	3	6	15	50	4000
* Average viscosity of 2 % aqueous solution at 20 °C					

COMPARATIVE EXAMPLE: Preparation of Itraconazole-Containing Pharmaceutical Composition 14

10 The same procedure as in Example 1 was conducted to prepare an itraconazole-containing pharmaceutical composition, except that 100 g of Eudragit ETM, a pH-dependent polymer, was used instead of 100 g of methylcellulose.

15 EXAMPLE 14: Average Particle Size of Itraconazole-Containing Pharmaceutical Composition and Properties of Powder Thereof

In order to determine optimal spray-drying conditions, the spray-dried products (particles) were measured for particle size distribution in various spray-drying conditions by use of a size distribution analyzer (Mastersizer/2TM). The experimental condition is shown below.

20 a spray-drying injection rate of 40 ~ 700 ml/min,
a spray-drying pressure of 0.5 ~ 7 kg/cm²,
a spray-drying inlet air temperature of 90 ~ 250 °C,
25 a spray-drying outlet temperature of 40 ~ 150 °C, and

a solid content of the spray-drying solution of 0.5 ~ 20.0 %.

According to the result using various spray-drying conditions, a broad distribution of particle sizes ranging from tens of nm to tens of μm was obtained. Therefore, controlling spray-drying conditions could change particle sizes of the spray-dried products. Particularly when the spray-drying process was conducted under the following conditions, the particle size of the spray-dried products fell within the range of 1 to 10 μm .

a spray-drying injection rate of 50 ~ 60 ml/min,
a spray-drying pressure of 3 kg/cm²,
a spray-drying inlet air temperature of 105 ~ 115 °C,
a spray-drying outlet temperature of 55 ~ 65 °C, and
a solid content of the spray-drying solution of 5.2 %.

Data obtained in above examples show that smaller particle size of the spray-dried product is obtained at higher spray drying pressures with lower solid contents of the spray drying solution. It was also revealed that, at higher inlet and outlet temperatures, it was improved in the flowability of particles, but resulted in increasing the bulk density of the particles. It was reported that the specific area of smaller particle size is larger so that their dissolution rate or solubility is increased. In the present invention, however, spray-dried products containing fine particles of several nm are rather decreased in solubility owing to inter-particulate agglomeration or aggregation.

EXPERIMENTAL EXAMPLE 1: Solubility of Itraconazole

The pharmaceutical composition particles prepared in Examples 1 to 13 and the Comparative Example were measured for solubility in buffer solution of pH 1.6 and pH 2.4 at 37 °C. The results are given in Table 3, below. For comparison, commercially available itraconazole-containing products, such as Sporanox™ capsules and Sporanox™ tablets were used.

TABLE 3

Solubility of Itraconazole-Containing Pharmaceutical Compositions

Example	Solubility (µg/ml)		Solubility ratio (pH 1.6/ pH 2.4)
	pH 1.6	pH 2.4	
1	61	1	61.0
2	62	11	5.6
3	58	3	19.3
4	52	3	17.3
5	52	2	26.0
6	59	8	7.4
7	60	8	7.5
8	55	7	7.9
9	58	5	11.6
10	62	11	5.6
11	149	70	1.7
12	149	69	2.2
13	130	51	2.5
Comparative example	63	14	4.5
Sporanox™ capsules	85	16	5.3

Sporanox™ tablets	65	25	2.6
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As apparent in the above results, the solubility of itraconazole was greatly improved when it was used together with water-soluble polymers in accordance with the present invention than when it was used alone (solubility 1 µg/ml or less). In particular, cellulose derivatives brought about a larger increase in solubility.

Polymers with higher average viscosity, that is, higher average molecular weight, resulted in greater solubility. However, too high viscosity made it difficult to spray-dry the solution and deteriorated the flowability of the produced particles, as well as reduced the increment in solubility. Therefore, the average viscosity of the polymers used was preferably in an appropriate range.

In particular, the pharmaceutical compositions of Examples 11 and 12 are absolutely improved the solubility, as well as showed only a small difference of solubility between pH 1.6 and pH 2.4. Both of the pharmaceutical compositions prepared in Examples 11 and 12 showed the solubility ratio by only two times between pH 1.6/pH 2.4, compared to the those of pharmaceutical compositions of the other examples, which were five times. Therefore, these results indicate that the itraconazole-containing pharmaceutical compositions of the present invention surmount the absorption difference of itraconazole resulting from the characteristic pH fluctuation which occurs within the stomachs of normal adults, as well as improving the absolute absorption of itraconazole and minimizing the

intra- or inter-individual variation of gastrointestinal physiology.

On the other hand, when Eudragit ETM, a conventional pH-dependent polymer, was used, the solubility of itraconazole was greatly decreased on the whole, compared to the present invention. When using Eudragit ETM, it decreased the solubility of itraconazole by a factor of two times at pH 1.6 and by a factor of seven times at pH 2.4, compared to the present invention and showed the solubility ratio by four times or more between pH 1.6/pH 2.4, which indicates that a great change in solubility results from even a small change in pH. Therefore, it is difficult to determine administration conditions for itraconazole, as well as predict its therapeutic effects when formed with pH-dependent polymers, as they cause the drug's solubility to greatly vary with normal fluctuations of gastric pH.

As for commercially itraconazole-containing products, SporanoxTM tablets and SporanoxTM capsules, their solubility at pH 1.6 and pH 2.4 are three times lower than those of the pharmaceutical composition of the present invention at corresponding pH values. In addition, the solubility ratio showed five times or more between pH 1.6/pH 2.4, that is, the solubility of itraconazole in conventional drugs at pH 1.6 is increased by five times or more, compared to that at pH 2.4. Consequently, the itraconazole-containing pharmaceutical compositions of the present invention can be suggested as alternatives which surmount the disadvantages of conventional formulations.

EXPERIMENTAL EXAMPLE 2: Dissolution of Itraconazole-Containing Pharmaceutical Compositions

Pharmaceutical compositions prepared in the above examples were formulated into such tablets as not to cause disintegration problem and then, measured to a dissolution test in pH 1.2 buffer solutions. After a lapse of 30 min, dissolution rates of 85 % or higher were found in most of the compositions. However, the pharmaceutical compositions of Examples 6 and 13, which employed polymers of high average molecular weight or average viscosity, made difficult their formulation into tablets so high viscosity that resulted in relatively poor in dissolution rate.

EXPERIMENTAL EXAMPLE 3: *in vivo* Bioavailability Test of Itraconazole-Containing Pharmaceutical Composition

The pharmaceutical composition of Example 11 with an itraconazole content of 100 mg was orally administered to ten healthy adults from whom blood samples were then taken at 0.5, 1, 2, 3, 4, 5, 6, and 8 hours after the administration, to measure blood levels of itraconazole. This quantification was conducted in both fasted state and fed state. The results are given in Table 4, below.

TABLE 4

Blood Level of Itraconazole

Hour	Level in blood (ng/ml)	
	Fasted state	Fed state
0.5	39(47)*	17(19)

1	100 (115)	39 (34)
2	151 (92)	110 (98)
3	153 (62)	132 (97)
4	131 (45)	162 (102)
5	96 (35)	150 (60)
6	86 (33)	140 (60)
8	69 (27)	114 (49)
Average, C _{max}	175 (93)	186 (88)
Average, AUC**	816 (387)	934 (476)
*() represents standard derivation. ** AUC : Area Under the Curve		

When being administered via an oral route, as seen in the data of Table 4, the itraconazole-containing pharmaceutical compositions of the present invention showed almost the same values in both C_{max} (maximal level in blood) and AUC (area under the curve), which are indexes for drug bioavailability, irrespective of taking of meals. SporanoxTM capsules, commercially available products, were found to be decreased in bioavailability by two times when being administered before meals as compared with when being administered after meals. Considering that this product is recommended to be administered after meals, the above results demonstrate that the itraconazole-containing pharmaceutical compositions of the present invention are significantly improved in *in vivo* absorption. That is, the itraconazole-containing pharmaceutical composition of the present invention has high bioavailability as proven by its high solubility at the gastric pH of a fasted state.

As explained hereinbefore, the itraconazole-containing pharmaceutical composition of the present invention increases the solubility of itraconazole and prevents the reduction of solubility of itraconazole caused as pH
5 increase, thereby improving its *in vivo* absorption. By reducing the bioavailability difference of itraconazole, which is attributed to the characteristic intra- or inter-individual gastric pH fluctuation and to food intake, the compositions of the present invention are effectively
10 applied to normal adults as well as hypoacidic normal persons or AIDS patients. In addition, the methods for preparing itraconazole-containing pharmaceutical compositions in accordance with the present invention adopt a single spray-drying process such that it can be readily
15 industrialized and controlled the physical properties of drug particles to the most suitable conditions for *in vivo* application.

What is claimed is:

1. An itraconazole-containing pharmaceutical composition,
obtained by spray-drying the solution in which an
5 itraconazole and a pH-independent water-soluble
polymer are dissolved into a solvent.
2. The composition as set forth in claim 1, wherein the
amount of pH-independent water soluble polymer used
10 is in the range of 10 to 1000 part by weight based on
the itraconazole.
3. The composition as set forth in claim 1, wherein the
pH-independent water soluble polymer is selected from
15 the group consisting of cellulose derivatives,
including methyl cellulose, ethyl cellulose,
hydroxymethyl cellulose, hydroxyethyl cellulose,
hydroxyethylmethyl cellulose, hydroxypropylmethyl
cellulose, carboxymethyl cellulose, sodium
20 carboxymethyl cellulose and carboxymethylethyl
cellulose; polyvinyl alcohols; polyvinylpyrrolidone
or copolymers thereof; polyvinylacetate;
polyalkeneoxide or polyalkeneglycol; polyethylene-
polypropylene copolymers; polyoxyethylene-
25 polyoxypropylene copolymer (Poloxamer); and
combinations thereof.
4. The composition as set forth in claim 1, wherein the
pH-independent water soluble polymer has an apparent

average viscosity of 1 to 1,000 cps in a 2 % aqueous solution at 20 °C.

- 5 5. The composition as set forth in claim 3, wherein hydroxypropylmethyl cellulose, hydroxypropyl cellulose or methyl cellulose has an apparent average viscosity ranging from 10 to 60 cps in 2 % aqueous solutions at 20 °C.
- 10 6. The composition as set forth in claim 1, further comprising at least one pharmaceutically acceptable additive selected from the group consisting of salts including sodium chloride; saccharides including white sugar and lactose; excipients including finely
15 crystallized cellulose, calcium hydrogen phosphate, starch and mannitol; and/or lubricants including magnesium stearate, talc, glyceryl behenate and colloidal silica.
- 20 7. The composition as set forth in claim 1, wherein the size of the spray-dried particle is from 10 nm to 1000 µm.
- 25 8. A method for preparing an itraconazole-containing pharmaceutical composition of claim 1, comprising the steps of:
- 1) dissolving into a solvent itraconazole, a pH-independent water-soluble polymer and a pharmaceutically acceptable additive; and

2) spray-drying the obtained solution under the conditions including:

- a spray-drying injection rate of 40 ~ 700 ml/min,
- a spray-drying pressure of 0.5 ~ 7 kg/cm²,
- 5 a spray-drying inlet air temperature of 90 ~ 250 °C,
- a spray-drying outlet temperature of 40 ~ 150 °C, and
- a solid content of the spray-drying solution of 0.5 ~ 20.0 %.

- 10 9. A dosage form of the itraconazole-containing pharmaceutical composition of claim 1 formulated into a tablet, a coated tablet, a hard capsule, a soft capsule, suspension, suspended syrup, dry syrup, a paste, an solution or a spray.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR01/00657

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 A61K 9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA Online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 9857967 A1 (DONG-A PHARMACEUTICAL CO.) 23. December 1998 (23. 12. 1998) see abstract, examples and claims; cited in the application.	1-9
Y	WO 9933467 A1 (CHOONGWAE PHARMA Co.) 08. July 1999 (08. 07. 1999) see entire document.	1-9
P, X	WO 2001041765 A1 (DONG-A PHARMACEUTICAL CO.) 14. June 2001 (14. 06. 2001) see entire document.	1-9

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9857967 A1	23. 12. 1998	AU 9879392 A1 EP 991646 A1 BR 9810124 A	01. 04. 1999 12. 04. 2000 08. 08. 2000
WO 9933467 A1	08. 07. 1999	AU 9915113 A1 EP 1039909 A1	19. 07. 1999 04. 10. 2000